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The pathology and prevention of influenza



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March, 1898.



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PATHOLOGY AND PREVENTION
OF
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S. T. Armstrong
New York, 1892

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BY

JULIUS ALTHAUS, M.D., M.R.C.P., LOND.,

*Senior Physician to the Hospital for Epilepsy and
Paralysis, Regent's Park.*



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THIS little book is an amplification of a paper on the Pathology of Influenza, which I read before the Medical Society of London, on November 2nd, 1891, and which appeared in the *Lancet* for November 14th and 21st, 1891.

48, HARLEY STREET,
November, 1891.

THE PATHOLOGY AND PREVENTION OF INFLUENZA.

I PURPOSE to show in this paper that the symptoms of influenza are owing to the action in the system of a special poison secreted by a pathogenous bacillus ; that this poison has a special affinity to a definite centre of the nervous system, which is irritated and depressed by it ; that an antidote which is able to neutralise the effects of the poison is formed in the blood of the patient, and tends to effect a spontaneous cure of the disease ; and that the nearest approach to this antidote which we at present possess appears to be animal vaccine-lymph, which should therefore be used as a preventive of influenza, in case another epidemic of that distemper should break out in the country.

The word "influenza" being somewhat long and, as it seems to me, not very happily chosen, I have in the present paper frequently used the term "grip," by which the disease is known in Germany and France, but spelt as an English word, as synonymous with influenza. I

hope that this innovation may be generally accepted, not only because the term is short, but also because it graphically denotes the suddenness with which the disease attacks the patient. I remember having had grip as a boy, during the epidemic of 1849, and can well recall the utterly unexpected and rapid manner in which I was seized with fever and dreadful pain in the head and the body, having felt quite well only an hour before. Another reason for accepting the term "grip" as equivalent to influenza is, that it is really impossible to speak of the "influence of influenza," as one often feels tempted to do when talking or writing about it, while the "influence of grip" may pass muster anywhere.

There can be no doubt that the epidemics of grip of the years 1889-91 have been the most interesting medical event of late years, and that they have taught us a great many lessons which we did not know before. Indeed, the disease not having appeared in England in an epidemic, or, rather, pandemic form for many years past, was unfamiliar to the present generation of practitioners; more especially as in numerous cases the signs of catarrh of the respiratory organs, commonly called "influenza cold," and which were generally believed to be characteristic of the complaint, were either slight or

completely absent, the most striking symptoms of the distemper having been in the majority of cases a sharp and short attack of fever, great physical and mental prostration, and severe pain in the head, body, and limbs, most or all of these symptoms ceasing as suddenly as they had appeared.

In accordance with our present views as to the mode in which infection takes place, I look upon the symptoms of influenza as due to the action in the system of a special toxine, secreted by a pathogenous bacillus. I regret to say that the results of numerous and laborious researches made by competent observers on the bacteria of grip flatly contradict each other, and that nothing definite is as yet known about the morphology of that micro-organism, nor about the chemical constitution of its poisonous secretion. Neither Weichselbaum's lancet-shaped diplococcus, nor Klebs's flagellated monads, nor Vaillard and Vincent's streptococcus, nor Kirchner and Seifert's punctiform microbes, have stood the test of criticism; and it seems probable that different modes of investigation will have to be invented before the real culprit can be discovered. All I feel it prudent to advance with regard to these points at present is, that the life-duration of the bacillus seems to be in the

majority of cases a short one, inasmuch as the stage of incubation of the malady does not appear to last longer than two, or at the outside, three days, and the attack of the disease from two to fifteen days, while the patient may remain a focus of infection to others for about a week or ten days longer. On the other hand, the virulence of the toxine secreted by the parasite appears to be most remarkable, causing, more especially when it falls on a suitable soil, an immense variety of severe symptoms, not only during the primary attack, but also in many cases for a long time subsequently, and leading not unfrequently to a fatal issue, or to such destructive lesions of important organs as tend to disable the patient for life. Experience has indeed shown the popular belief that "influenza is not much of a disease," to be utterly fallacious, and it is regrettable to find that such an erroneous notion is shared by members of our own profession. Thus Broussais stated as recently as December, 1889, in a paper published in the *Revue Générale de Clinique et de Thérapeutique*, that influenza "was an invention of needy people, of doctors without patients, whose time hung heavily on their hands, and who had amused themselves with inventing such a bogey." Unfortunately this "bogey" has proved a fearful reality for

many people who have lost their lives or their health through it !

Why should the attack of grip end in some cases suddenly with profuse perspiration, and all the other symptoms of a crisis, leaving the patient weak, but really not much the worse for what he has gone through, while in other instances its course is much more protracted, and attended with dangerous complications and sequels ? It appears to me that we can give a tolerably plausible answer to this question by reference to what takes place in pneumonia, which has been much better studied in this respect than grip. In pneumonia, as in most other infectious diseases, it is not so much the circulation in the blood of a special bacillus—Fraenkel's diplococcus—which causes the disease, nor the number of these cocci present which kills, as the poison secreted by them. This poison has recently been isolated by G. and F. Klemperer, who found it to be an albuminoid amorphous yellowish-white powder, which they obtained by precipitating the diplococcus with absolute alcohol, thus killing the parasite, and then dissolving the precipitate in water and evaporating it. A solution of this toxine, when injected into rabbits, caused either death or severe febrile disturbance. It is the pneumo-toxine which, by

circulating in the blood, causes the fever and the consolidation of one or several lobes of the lung, and endangers life by depressing the vital energy of the nervous centres of respiration and the heart's action. After the pneumonia has lasted a few days, however, an antidote to the toxine is formed, either from the poison itself, or by its aid from the albumen of the serum. As soon as this anti-pneumo-toxine circulates in the blood, the crisis in pneumonia begins, and the anti-toxine eventually neutralises all the poison which the diplococcus has formed in the system. The serum of the patient thus becomes innocuous; the bacteria are, as it were, disarmed; the system regains its power of resistance, and the diplococcus presently perishes in the same way as other non-pathogenous micro-organisms, when injected into the blood of animals or men, perish rapidly by the action of the white blood-cells. It may however happen that the quantity of anti-toxine formed in the system is not sufficient for neutralising all the toxine which is in circulation, and then there will be only a pseudo-crisis, the fall of temperature being slight and temporary. Again, if anti-toxine remains in excess after the crisis is over, the patient thereby acquires at least temporary immunity;

this latter may, however, subsequently be lost again by the disappearance of anti-toxine from the serum. Such immunity may be extended to animals; for rabbits which had been infected with pneumo-toxine, and which otherwise would inevitably have died of it, recovered their health when injected with serum from a patient who was just passing through the crisis of pneumonia. Finally if a solution of toxine was mixed with curative serum, and then injected into animals, no effect was produced, showing that the poison had been neutralised by the addition to it of serum containing anti-toxine.

Let us now apply the results of these researches to influenza, which appears justifiable on account of the similarity of the morbid processes in the two diseases. I assume, then, that the patient having acquired infection, a poisonous albuminoid secreted by a special pathogenous bacillus, and which I will call the *grippe-toxine*, circulates in the blood, and causes the special symptoms of the feverish attack. In a day or two, however, an antidote, which I will call the *anti-grippe-toxine*, is formed in the serum of the patient. Now let us suppose the quantity of this anti-toxine to be, in a given case, sufficient for neutralising all the toxine which is circulating in the blood; and there will be, as a natural

consequence, a crisis, with a sudden considerable fall of temperature, profuse perspiration, and relief to the distressing subjective symptoms. If, however, the quantity of the anti-grippo-toxine formed in the serum should be too small to neutralise all the toxine which may be present, the course of the disease will be protracted, there will be only a pseudo-crisis, and complications and sequels of different kinds will follow.

By the aid of this theory we may also explain why *immunity*, which has been acquired by a patient, may subsequently be lost again. Let us suppose that all the anti-grippo-toxine which has been formed in the serum, has been lost, and that the patient is again exposed to infection. A second or even third attack of grip may then take place in the same individual, just as we meet occasionally with a second or third attack of measles, pneumonia, or rheumatic fever, in the same patient. The theory which I have just proposed therefore appears to explain satisfactorily:—

- 1st. Why patients acquire influenza ;
- 2nd. Why they recover from it, either perfectly or imperfectly ; and
- 3rd. Why, after having had it once, they contract it again a second or third time.

I now proceed to the next portion of my subject, which is to show that all the symptoms of the feverish attack of influenza are referable to irritant poisoning of a definite centre of the nervous system. Let me first show you the steps by which I have arrived at this opinion.

Shortly after the visitation of influenza had commenced, I was surprised to find, both in hospital and private practice, a number of patients complaining of severe forms of neuralgia, loss of power, and a general break-up of the nervous system, which they attributed to an attack of grip which they had recently passed through. I was also re-visited by some of my former patients who had for years past remained free from certain nervous affections to which they had previously been subject, but who had seen their old troubles suddenly revived during or after convalescence from grip. Amongst the fresh cases which presented themselves, I found that the state of health of the patients had in a good many instances been quite satisfactory before influenza had laid hold of them, so that this latter appeared to be *fons et origo mali* altogether ; while in others a neurotic pedigree, or a previous syphilitic infection, or some other constitutional fault, could be clearly traced, upon which

the subsequent nervous affection had as it were been grafted.

It also soon became evident to me that the number of nervous sequels which appeared after grip was largely in excess of other post-febrile neuroses, of which I had seen numerous examples in the course of my practice. In comparing those nervous troubles which may be met with after such diseases as diphtheria, typhoid fever, scarlatina, small-pox, measles, erysipelas, and malaria, with those seen after influenza, none of the former, nor indeed all of them put together, approached in number the nervous sequels of grip.

I could not help being very much impressed with these facts, of which there were only few indications to be found in medical literature, more especially as soon afterwards numerous papers appeared in British and foreign medical journals, describing cases of nervous disease showing the same origin. On reflecting about this matter I came to the conclusion that one reason why the number of neuroses, seen after grip, is so very largely in excess of those observed after other acute diseases, was that more than half the population of the country had latterly been down with influenza, while the number of patients suffering at any one period from other fevers, is always

very much less. It soon, however, became evident to me that there was not only a greater number, but also a far greater variety in the nature and aspects of the nervous sequels of grip, than in those of other infectious fevers.

We all know the character of the post-febrile neuroses seen after such diseases as diphtheria, small-pox, and typhoid fever, to mention only some of them; and we are agreed that they run in comparatively narrow grooves. Thus we see local palsies arising from peripheral neuritis, and occasionally aphasia and hemiplegia, and certain diseases of the spinal cord, after typhoid fever. Again, we meet with paralysis and anæsthesia of the soft palate, paresis of accommodation, ophthalmoplegia, and what Dr. Guthrie has recently called "bulbar crises," after diphtheria. But who has seen such different diseases as optic neuritis, optic atrophy, supra- and infra-orbital neuralgia, embolism of the central artery of the retina, spasmodic torticollis, tetany and tetanus, stammering and hysteria, astasia and abasia, diabetes and tachycardia, after small-pox? Or who has met with agoraphobia and catalepsy, Jacksonian epilepsy and Graves's disease, chorea and angina pectoris, unilateral and bilateral paralysis of the portio dura, general paralysis of the insane, melancholia, and other

psychoses, after diphtheria? Yet all these and other nervous affections have been observed as direct and unmistakable sequels of influenza; and I have no hesitation in stating that there are few disorders or diseases of the nervous system which are not liable to occur as consequences of grip, and that as a powerful etiological factor of protean forms of nerve-disease, influenza stands *facile princeps* amongst all infectious fevers.

The only distemper which approaches grip in this particular quality is *syphilis*, which may also give rise to the symptoms of almost any nervous disease with which we are acquainted. I find a still further analogy between these two infectious diseases in the circumstance that in both we may have a primary attack, secondary symptoms of a comparatively mild character soon afterwards, and tertiary affections of a more dangerous and obstinate nature, affecting the organic structure of tissues at a more remote period.

Influenza also appears in a number of cases to revive an old syphilitic infection which has been dormant in the system for years, and thus indirectly to give rise to certain diseases of the spinal cord, which are known to occur habitually on a syphilitic base. In comparing the degree of virulence of the two poisons, however, I have found

that, when the grippo-toxine attacks the structure of organs, it often does so with far greater ferocity, and in a more ruthless manner than the syphilitic virus. Thus we sometimes see incurable blindness from optic atrophy established within a few days of the outbreak of the feverish attack of influenza, while, when the same affection is owing to syphilis, its course is generally protracted over years, and it is also more amenable to treatment. Again, I have seen spastic paralysis, when owing to grip, striking the patient down with one fell blow ; while the same disease, when owing to syphilis, is slow in development, and apt to be arrested in its progress, and improved in its symptoms by therapeutics. Finally I have known general paralysis of the insane to come on after an attack of grip, in men who had previously been perfectly well, to destroy the patient's physical and mental powers, and to end fatally within a few months ; while when owing to syphilis, I have seen the course of the same disease extending over six or seven years. In almost all neuroses which occur on a syphilitic base, we have a reasonable chance of doing good by treatment, while organic brain or cord affections consequent upon influenza, seem often to be utterly incurable from the first.

When I had once realised this extraordinary tendency of grip to be followed by nervous sequels of almost any description, it was only a short step to the further enquiry whether the chief reason of this peculiarity might not be found, independently of the great prevalence of the parent disease, in the circumstance that the distemper itself, in its primary manifestations, is not so much an infectious catarrhal fever, as has been generally assumed, as an infectious *nervous fever*? A clinical survey of the symptoms of the feverish attack rendered this *primâ facie* not unlikely, as many of them point unmistakably to the nervous system as the starting-point. Such signs are a peculiar kind of fever, severe headache and back-ache, neuralgic pain in the body and limbs, utter prostration of mental and bodily strength, and insomnia, to which in many cases are added delirium, coma, convulsions, paralysis, deafness, loss of smell and taste, etc., while, on the other hand, catarrh of the mucous membranes and inflammation of the lungs, have been completely absent in a large proportion of cases. Indeed, many patients have had influenza badly, without having once sneezed or coughed. Again where catarrh and pneumonia were present, these have frequently assumed such a peculiar character as to lead to the

suspicion that they might likewise arise from irritation of, or loss of power in, the various nervous mechanisms supplying the affected parts, and would therefore have to be looked upon more as vasomotor and trophic neuroses than ordinary catarrh and inflammation.

With regard to this latter point, it is interesting to note that Graves, the greatest master whom the Dublin school has produced, had already, as far back as 1883, expressed his conviction that the poison of influenza acted on the nervous system in general, and on the pulmonary nerves in particular. In many bad cases of bronchitis and pneumonia accompanying influenza, Graves had found the dyspnoea to be intermittent, and undergoing remarkable exacerbations and remissions at certain hours of the day and night, rendering it likely that the affection of the bronchial tubes and lungs was of a nervous character.

The great varieties observed in the symptoms of the feverish attack of grip, in the recent, as well as in the older epidemics of it, have induced a number of observers to assume three different forms of the disease, viz. :—

- 1st. The nervous or encephalic form ;
- 2nd. The catarrhal, respiratory, or thoracic form ; and
- 3rd. The gastro-intestinal or abdominal form of grip.

We have good descriptions of these different forms from the pens of Brochin, Leyden, Bidon, and others; and a computation made by collecting a large number of cases which have occurred during the recent epidemics in the practice of a number of observers, would appear to show that 55 per cent. belonged to the so-called nervous form, 30 per cent. to the catarrhal form, and 15 per cent. to the gastric form.

I wish, however, to lay particular stress on what I am convinced to be the fact, viz., that these three forms of the disease are not distinguished from one another by any true pathological characters, but *that influenza is always a true nervous fever*, the symptoms of which differ only as far as localisation of the grippo-toxine in different areas of the nervous system is concerned. Indeed it would be quite as easy to propose eight or ten different forms of the disease as the three which I have just mentioned, and which are perfectly arbitrary, however much sanctioned by authority. Being guided by the principle of localisation, I contend that the first or nervous form is that in which we have to do with the effects of the grippo-toxine upon the thermolytic, cardiac, and other centres in the medulla oblongata or bulb; that in the second or catarrhal form, the special

nervous mechanisms formed by the fifth pair and the pneumogastric nerves, which supply the mucous membranes of the eyes, the frontal sinuses, the nose, pharynx and larynx, the trachea, bronchial tubes and lungs, are suffering; and that finally in the third, the gastro-intestinal or abdominal form, the symptoms are owing to poisoning of those portions of the nuclei and branches of the pneumogastric nerves which supply the abdominal viscera, with occasional extension of the shock to the sphere of the splanchnic nerves which form a vasomotor centre for the whole abdominal cavity, and anastomose with the pneumogastric in the coeliac plexus. The argument which I will now endeavour to lay before you as concisely as possible, is at first sight supported by the clinical fact which has been frequently observed, that the three forms just mentioned are found to overlap and to be intermingled with each other, some of the symptoms peculiar to one form being seen in another, or one form gradually merging into the other as the disease progresses, showing that it is utterly futile to draw any strict line of demarcation between them. If I still adhere to that division, I do so simply for the sake of convenience in analysing the different groups of symptoms, and referring them to different areas in the nervous centres.

1.—Nervous Form.

One of the most important symptoms of this form is the fever, which shows considerable peculiarities. But before discussing this, let me ask the question: Are there any afebrile cases of influenza? This is a difficult question to answer in a positive manner; yet we have probably all seen, at the time of the epidemic which we have recently passed through, affecting as it did thousands of persons in our vicinity, a good many people who, without being actually laid up with definite symptoms of grip, yet seemed to some extent to be under the influence of the poison, as shown by such symptoms as general languor and depression, utter want of interest in what was going on, insomnia, headache and back-ache, constipation of the bowels, flatulence, etc. Sometimes there has been, as Sherman Bigg has recently pointed out, such unendurable despondency as to make the patient feel that death was preferable to the state in which he found himself, and suicide the only means of relief. I have seen one such case in a member of our own profession where the patient made three determined attempts on his life, each of which succeeded as nearly as possible. I have also seen a peculiar form of neuralgia, coming on quite gradually, without any apparent cause, affecting

chiefly the supra-orbital and infra-orbital nerves, the brachial plexus, and the sciatic, that is to say, just the very nervous areas in which the grippo-toxine loves to localise itself, either in the attack or during convalescence. I have also known the lightning pains and other symptoms of tabes to be considerably aggravated, causing the patients to make themselves drunk with alcohol or morphine, in order to find relief. In connection with this I may allude to a singular observation made in the Deaf and Dumb Institution in Copenhagen, where the pupils have been regularly weighed daily for the last seven years, and where it was found that the increase of body-weight, which habitually takes place during the months of November and December, did not occur in 1889, when influenza raged in the Danish capital. Yet none of the pupils had had grip, while six of the professors were ill with it, and may on their return to work have brought some germs of the disease into the place, and thereby depressed the vital powers of the pupils. I am inclined to ascribe all these singular occurrences to a *chronic infection of the nervous system with the grippo-toxine*, which may occasionally, although no feverish attack has taken place, entail serious consequences upon those affected by it.

To return, however, to the consideration of the *fever* in grip. The rise of temperature is generally sudden, running up to something between 100° and 103° within a few hours, and being accompanied with chilly feelings or regular rigors, followed by, or alternating with, heat. Cases, however, are not uncommon in which a much higher degree of fever is reached. Many practitioners have seen 106° , and I have heard of a case in which the illness began with coma and a temperature of 108° ; the day after the body-heat was normal, and the patient practically well. A patient who consulted me lately for nervous sequels of grip, informed me that she had for two days a temperature of 109° , yet the nerve-trouble from which she suffered afterwards was of a mild character. I mention these cases in order to show that there is no parallelism between the degree of fever and the severity of the illness, as in the case of the eruptive fevers and other acute diseases, and is therefore unimportant in a prognostic point of view. All of you must have seen cases of grip in which the temperature, however high at first, fell to the normal standard in less than twenty-four hours, with proportionate relief of the more distressing symptoms. Such a sudden fall of temperature has

often been ascribed to some doses of antipyrin or phenacetin, which have been given during the stage of pyrexia, but it has likewise occurred in numerous cases where no antipyretics or any other drugs had been administered.

In uncomplicated cases and otherwise healthy adults, the fever rarely lasts longer than one, two, or three days. It shows no definite type, as for instance in typhoid fever, but an extraordinary degree of mobility, being inclined to be irregular and intermittent. Where there is a persistent rise, or considerable fluctuations in it, after the second or third day, this is owing to unfavourable complications, or to the subjects being aged or weakly, or affected with pre-existing laryngeal, pulmonary, or renal affections. In such cases, therefore, the thermometer becomes an instrument of the greatest diagnostic and prognostic importance.

How is the fever to be explained by the neurotic theory of grip? This question is not easy to answer, because physiologists and pathologists are not yet agreed about a point of the first importance in the theory of fever, viz., whether the increased temperature is owing to increased *production* of heat, or to diminished *loss* of it, that is, increased retention. At the present time most

pathologists are in favour of the former alternative, and hold that the fever-heat is due to increased production of heat, this being caused by irritation of the thermo-genetic centre which Eulenburg and Landois, Ott, Hale White, and others have shown to reside in the corpus striatum, or, more strictly speaking, the caudate nucleus. This grey centre is known to control the oxidising metabolism which is constantly going on in the substance of the voluntary muscles, which constitute indeed the laboratory where the body-heat is produced. In the caudate nucleus there is a double nervous mechanism which in health acts harmoniously together, one set of nerves being excitor, while the other is inhibitory or regulating. Now it is assumed that in fever the excitor nerves are unduly active, causing excessive destructive metabolism, while the inhibitory nerves are paralysed, and unable to exert their controlling function. Macalister indeed states quite plainly that the fever-heat is due, not to continuously diminished discharge, but to greatly increased production of heat.

I have long been of opinion that the opposite contention, first put forward by Traube, of Berlin, in 1863, is nearer the truth, viz., that the fever-heat is not owing to increased production, but to *increased retention of heat*. Traube referred pointedly to such symptoms as rigors,

the pale and cold skin, the subjective feeling of chill which is experienced where the thermometer has already shown a rise, etc. This theory has quite recently received considerable support from the experiments of Rosenthal, of Erlangen, who caused fever in cats by hypodermic injections of such substances as pyocyanine,¹ an infusion of hay, tubercular sputum, and others. He then produced a rapid fall of temperature by injections of antipyrin, and used in his researches a highly sensitive air-calorimeter. Rosenthal has arrived at the conclusion that in the first stage of fever, when the temperature begins and continues to rise, the increased heat is invariably due to increased retention, and not to over-production. When the fever is at its height, there appears to be a difference with regard to different kinds of fever, but in a number of cases the heat is, in this stage likewise, owing to increased retention. Finally, in the stage of defervescence, he has found that the loss of heat by the skin and lungs was enormously increased, and that the degree of this loss corresponded very closely to the fall of temperature which was observed.

¹ Pyocyanine is a sterilised solidified pure culture of the bacillus pyocyaneus.

Assuming these experiments, which appear to have been most carefully made, to be correct, I would explain the fever-heat in grip, not by irritation of the thermogenetic centre in the caudate nucleus, but by congestion of the thermolytic centre in the medulla oblongata, upon which the grippo-toxine acts as an irritant poison. This centre regulates the loss of heat which is constantly taking place through the skin and lungs, and includes for this purpose the vaso-constrictor centre which controls the action of the blood-vessels of the skin, the sudoriparous centre which presides over the action of the sweat-glands, and the respiratory centre which regulates the movements of the lungs (Hale White). There are centres for all these organs and functions in the entire extent of the spinal cord, but the head-centre, if I may borrow that expression from Fenianism, is for one and all in the bulb. The question might be asked whether the thermotaxic centre, which is intended to adjust the balance between the two centres of heat-production and heat-loss, has any special connection with the fever of grip? This centre, which appears from the most recent researches of Ott, to be situated in the tuber cinereum, in the anterior part of the floor of the third ventricle, is more complex and evolved at a later period, and is for this reason more easily put

out of gear than the two other centres. I do not, however, see any reason to believe that it plays any considerable part in the production of the fever of grip, which seems to be more satisfactorily explained by the morbid irritation and congestion of the thermolytic centre in the bulb. As long as this centre continues to be irritated by the grippo-toxine circulating in the blood, the fever continues; but as soon as so much anti-toxine has been formed in the serum as is required for neutralizing the action of the toxine, there is a crisis, with a sudden fall of temperature, profuse diaphoresis, loss of heat through the skin and lungs, tendency to sleep, and relief of other symptoms. This crisis is occasionally accompanied with a scarlatina-like rash on the face, body and limbs.

As in some other febrile diseases, it is noticed in grip that those cases do best in which a tolerably high fever is followed by profuse perspiration and sudden loss of heat, while those cases in which the fever has a protracted course, and terminates by lysis rather than crisis, are more likely to have a tedious and prolonged convalescence, and to be followed by severe complications and sequels. In this latter class of cases, we may suppose that an insufficient quantity of anti-toxine has been formed in the serum, with the result that the pathogenous

bacillus is not rendered innocuous, but allowed to continue its mischievous career in the system.

I have just referred the fever of grip to *congestion* of the thermolytic centre in the bulb. Indeed, no one who has watched and considered the clinical symptoms of the feverish attack of grip will deny that congestion must be looked upon as the principal pathological process which is at work during that time in the system. It is true that the symptoms are often so severe as to indicate *primâ facie* inflammation. More especially in children, influenza not unfrequently begins with what looks like symptoms of meningitis. There is intense headache, vomiting, constipation, grinding of teeth, rigidity of the neck, convulsions, delirium, and coma. In some cases the child becomes unconscious so suddenly that it looks like a stroke of apoplexy; yet the sudden defervescence of the most alarming signs, which is noticed sometimes twenty-four or thirty-six hours after their commencement, renders it certain that there can have been no inflammation or effusion, which require a much longer time for their resolution or absorption. Congestion, on the contrary, we know to be liable to very sudden modifications and variations under the influence of various agents, or after the cessation of certain causes. This opinion gains

considerable support from the fact that in cases which looked like meningitis, a sudden improvement has often ensued in consequence of profuse epistaxis setting in. Moreover, we actually *see* congestion in that suffusion of the conjunctiva and swelling of the eyelids which are met with almost invariably in grip.

Inflammation, however, does occasionally occur in various organs in particularly severe cases of influenza, when the irritation of the vaso-constrictor centre in the bulb by the grippo-toxine reaches a very high degree. That such is really the case has not unfrequently been verified by post-mortem inspection. Meningitis and meningo-myelitis have been seen by Fraser, Mackay, Bäumlér, Leyden, Guibout, and others. Dr. Bristowe has described two cases of cerebral abscess following influenza, and has seen three other similar cases which ended fatally, and where the symptoms were such as to suggest that cerebral suppuration had supervened. Inflammation of all the structures of the eyes have been seen by a number of competent observers, more especially in France and Germany, and in this country by Mr. Macnamara, who drew attention to cases of double optic neuritis after influenza in his opening address at the section of Ophthalmology, during the last meeting of the

British Medical Association at Bournemouth. There are also records of cases of glossitis, otitis, peritonitis, thyroiditis, endo- and myocarditis, nephritis, and orchitis in connection with grip; and I explain these inflammations by the presence of an unusually intense degree of irritation in the vaso-constrictor centre in the bulb. The occurrence of some of the more specific inflammations, such as erysipelas and pneumonia, in which special bacteria are known to be the exciting agents, is however more probably owing to the circumstance that the power of phagocytosis is lost in consequence of the illness, and that those bacteria which are in health habitually destroyed by the leucocytes, whenever they make their appearance at the entrance-gates of the system—*quærentes quem devorent*—are then readily admitted and allowed to multiply in the blood, when they will cause their own specific inflammations.

Next to the fever the most common symptom in the nervous form of grip is *headache*, which comes on suddenly, and is often at once so intolerably severe that the patient instinctively seeks his bed. The pain is generally localised in the frontal region and the orbit, or the temples; sometimes however it is occipital, or extends all over the head. When affecting the orbit, any move-

ment of the eyes causes extreme suffering. The pain is sometimes of a dull and heavy character, but is more frequently described as stabbing, throbbing, bursting, racking, or as if blows were dealt with a hammer. It is generally combined with hyperæsthesia of the skin of the head and neck, and aggravated by contact, pressure, or movements. The pain is continuous, but apt to be worse at night, and generally lasts two or three days; yet it may continue for two or three weeks, and more.

I consider the headache to be owing, in the majority of instances, to congestion of the membranes of the brain and of the sensitive portions of the cerebral substance, which is in its turn consequent upon irritation of the vaso-constrictor centre in the bulb. Where the headache is particularly intense and prolonged, it may be due to inflammation of the parts just mentioned. In Bristowe's two cases of cerebral abscess which I have already mentioned, intense and constant headache, which lasted throughout the course of the illness, was one of the principal symptoms. Where the pain is unilateral and of the neuralgic type, with tenderness of certain points in the anatomical distribution of the affected nerves, I assume it to be owing to neuritis, or to a high degree of

congestion of the peri-neurium of the fifth nerve. In some cases it appears to be seated more in the muscular substance, for instance, of the occipito-frontalis or the ocular muscles, and may then arise from myositis or congestion of the muscular fibres. Finally, when occurring in the catarrhal form, it may be owing to severe catarrh of the frontal sinuses—all of these processes however being dependent upon irritation of the medulla oblongata.

Headache is often associated with *back-ache*, affecting more particularly the loins, and may be so severe that, taken in conjunction with the high fever, suspicion is excited that the patient may be in the premonitory stage of small-pox. There is also habitually stiffness and soreness of the whole body, and pain in the hips and thighs, all of them being aggravated by movement. The pain in the limbs is often so severe as if all the bones were broken, reminding us of the break-bone or *Abu-Rakaba* of dengue. Tremor, twitches, jerkings, cramps, and torticollis may also be present. The patient either lies in a death-like stillness, in order to avoid any increase of pain by movement, or he is so restless and uncomfortable that he constantly keeps tossing about or changing his position.

Independently of these pains, we often meet with a more definitely neuralgic pain, following the anatomical distribution of certain of the spinal nerves, which latter may be found tender on pressure throughout their course. If the intercostal nerves suffer, there is, in addition to the pain and tenderness, a feeling of tightness and constriction of the chest, oppression and anxiety. The breasts, testicles, and coccyx have also been found to be the seat of neuralgia. In the upper extremities the median and musculo-spiral nerve are apt to suffer in the same way, while the ulnar nerve is spared. In the lower limbs, the sciatic nerve is often similarly affected. Together with this there may be great hyperæsthesia of the skin, muscles or bones.

All these different pains in the body and limbs may be traced to congestion or inflammation of the spinal membranes, and the sensitive portion of the substance of the cord, that is, the posterior columns and the posterior grey cornua, as well as of certain peripheral spinal nerves, such congestion or inflammation being again the direct consequence of bulbar congestion.

Delirium is frequent in the febrile stage of influenza, and sometimes consequent upon the headache, where this is very severe. The patient is then literally driven

mad with pain. In other cases the delirium is by itself the chief symptom which overshadows all the other signs of the attack, and may precede, accompany or follow, any of them. Kisch mentions the case of a servant-girl, aged 21, who had been perfectly well, and suddenly began to scream and talk nonsense, which went on the whole night. The next day influenza declared itself, when she became quieter, and was quite well again in four days. In other cases the delirium lasts much longer, and is generally of a violent character; the patient is apprehensive of being murdered, wants to jump out of the window or to fight those who approach him, or sings and prays incessantly.

In the alcoholic, grip may prove the exciting cause of delirium tremens. It has indeed been a matter of common notoriety that during the late epidemics of influenza, cases of delirium tremens have been unusually frequent. We have then the ordinary signs of this condition, more especially the terrifying delusions, superadded to the signs of grip. It assumes however a somewhat different character from that which it usually has, for it lasts habitually longer, and may go on for eight or ten days, while the ordinary form of it generally lasts only three or four days. Moreover, the ordinary form almost invariably

gets well, unless there should be a complication with pneumonia, erysipelas, meningitis, or injury to the head ; while the alcoholic delirium of grip often proves fatal.

Delirium also occurs in the so-called respiratory form of grip, together with bronchitis, broncho-pneumonia, and pneumonia. Now we do not see delirium with ordinary bronchitis ; and when it occurs in pneumonia, it is generally towards the end, when the patient is in a typhoid state, and assumes the muttering form, while in the catarrhal form of grip, and also in the gastro-intestinal form, it is usually of a violent character.

In other cases the psychosis assumes more the form of depression and melancholia. The patient refuses food which he sometimes believes to be poisoned, is in a state of profound apathy, and expresses weariness of life. In most of these cases there is persistent insomnia, or when sleep is obtained, it is short, unrefreshing, and disturbed by distressing dreams. In more severe cases there is somnolence which may continue throughout the attack, and deepen into coma. Indeed sometimes the attack commences and ends with coma. The delirium and insomnia are owing to congestion of the cortex of the brain, whereby the grey matter is irritated ; while

somnolence and coma must be referred to a more severe degree of congestion, whereby the brain-matter is actually compressed. Where the congestion affects the central convolutions of the motor area of the brain, we meet with convulsions or paralysis. Other symptoms of the feverish attack, such as subjective flashes of light, noises in the ears, giddiness, deafness, loss of smell and taste, numbness of the head and face, etc., may also be accounted for by congestion of the different nerves involved, all of them being dependent upon the central event, congestion of the vaso-constrictor centre of the bulb.

The last set of symptoms which may occur in the nervous variety of grip to which I have to draw your attention is a most serious one, inasmuch as they indicate imminent risk to life by sudden failure of power in the heart's action and in respiration. They are in fact cardiac and respiratory crises.

In some cases the patient complains of a constant feeling of giddiness, and faints away perhaps four or five times during the first day of the illness. The pulse is then either exceedingly frequent, small, and almost imperceptible, or it is slow, irregular, and intermittent. The face is pallid, the extremities are cold, and the skin

is covered with a cold sweat. The patient appears, as it were, overwhelmed by the poison, which he has no power to eliminate. A similar state of things is sometimes observed in cholera, more especially in the beginning of an epidemic, in diphtheria and scarlet fever. In grip a patient may suddenly die of syncope before he has time to re-act, or to develop pneumonia or meningitis. There may be no pain, but simply a feeling of deadly languor; he seems paralysed, gradually gets cold, and dies without a struggle. In other cases there may be præcordial pain, giddiness, and palpitations, followed by lethargy, stupor and death. Where the patient survives, the heart's action often remains unsatisfactory for weeks or months afterwards; the pulse may continue slow and irregular, or there is tachycardia with 240 or more beats in the minute. A simple change in the position of the head or the body, a slight effort, may even at a later period lead to a cardiac crisis, which requires the utmost vigilance on the part of the practitioner and the attendants to avert or to combat. In some of these cases there is no change in the heart's structure, while in others a low form of myocarditis or endocarditis may be developed. Pawinski has shown that patients who have previous to the attack of grip

suffered from heart disease, however slight, are more apt to be affected by cardiac crises than where the heart has been thoroughly healthy.

At other times a respiratory crisis may threaten the patient's life. Graves had already drawn attention to a peculiar kind of dyspnœa, which is not justified or explained by any stethoscopic signs, and which he therefore referred to an affection of the nervous system. There may be the symptoms of spasm of the glottis, great pain in the chest, a violent cough, the breathing is hurried and difficult, and regular attacks of dyspnœa or orthopnœa recur at regular intervals. With all this there is no bronchitis or pneumonia. Ferrand has well remarked that there appears to be sometimes a kind of paralytic atelectasis of the lungs through loss of elasticity in the alveoles and bronchial paralysis, as shown by feeble respiratory murmur in a portion of the lungs, exaggerated resonance, and increased vocal fremitus. Huchard, who calls this condition bronchio-plegia, mentions the case of a woman, 76 years old, who had a slight attack of influenza, during which she exposed herself to cold. The same evening she was taken with severe dyspnœa. There were a few slight tracheal râles, but no fever, bronchitis, or congestion of

the lungs. There was however progressive cyanosis and asphyxia, of which she died in a week.

To these symptoms another interesting sign may be added, viz., polyuria, and an extreme excess of phosphates in the urine. There may indeed be a kind of phosphatic diabetes, resulting probably from the rapid break-up of the phosphorus contained in the nervous structures.

The cardiac and respiratory crises which I have just described point so clearly to an affection of the cardiac and respiratory centres in the bulb, that I should be carrying owls to Athens if I were to insist on this self-evident explanation.

2. Catarrhal Form of Influenza.

I now proceed to speak of the second variety of grip, viz., the so-called catarrhal, respiratory or thoracic form, which I consider to be owing to irritation of the nervous mechanisms formed by the nuclei of the fifth and pneumogastric nerves in the bulb.

The peculiar feature of this variety is that we have in addition to the fever and other symptoms all the signs of catarrh affecting more or less the whole extent of the mucous membranes of the respiratory tract, viz., the frontal sinuses, the lachrymal glands and ducts, the con-

junctiva, the maxillary sinuses, the pharynx, Eustachian tube and cavity of the tympanum, the larynx, trachea and bronchial tubes, together with congestion of the lungs or broncho-pneumonia. In some of these cases there is much irritation and congestion, but only little catarrh, the principal symptom being a most severe and peculiar hacking cough, which resembles whooping-cough, and may persist a long time after all the other symptoms have disappeared. In most cases however there is a profuse discharge from all parts of the mucous membrane, more especially from the naso-pharynx, which is at first serous or sero-sanguinolent, and subsequently becomes purulent. The tonsils may slough away; there may be angina and aphonia, so that the patient is only able to whisper. This may be followed by cedema of the glottis, when the dyspncea is intense, the breathing hurried, the facial expression anxious, and the accessory muscles of inspiration are seen to work as hard as possible.

It will be seen from this description that the grippocatarrh of the upper portion of the respiratory organs differs considerably from ordinary catarrh affecting those membranes. In grip the inflammation extends to the frontal and maxillary sinuses, the conjunctiva, lachrymal

glands and ducts, pharynx, Eustachian tube and tympanic cavity, which does not habitually occur in ordinary catarrh. Moreover in grip the serous or sero-sanguinolent flow from the naso-pharynx is more profuse. There is generally headache, nausea, vomiting, and all or some of the symptoms of the nervous variety, such as vertigo, general hyperæsthesia, stupor, melancholia, insomnia and delirium, while the expression of the face denotes a greater degree of suffering than exists in ordinary catarrh.

The *bronchitis* of grip is also of a peculiar character, and different from ordinary bronchitis. It is generally very rapidly developed, and accompanied by a peculiar pain behind the sternum, and difficulty of breathing, which is out of proportion to the physical signs. When there is hardly any rhonchus or sibilus, the patient may breathe forty or fifty times in the minute, and seem on the point of being choked, while next day he may be a great deal better or apparently well. The bronchial congestion may, however, gradually merge into catarrhal or even capillary bronchitis, and is then apt to last very long, being accompanied by a more distressing and obstinate cough, and a more profuse purulent expectoration than takes place in ordinary bronchitis.

These differences are also strikingly marked in the

peculiar form of *pneumonia* which is apt to accompany or to follow influenza. It is true that we meet also with ordinary croupous pneumonia in these cases, when Fraenkel's diplococcus is found in the sputum from the beginning of the illness up to the crisis, but not afterwards. This form of pneumonia, however, I believe to be only indirectly connected with grip. The system being enfeebled by the invasion of an irritant poison loses its power of resistance, or to speak more definitely, of phagocytosis, and offers a favourable soil for the development and multiplication of the pneumo-coccus and other bacteria which are always present in the fluids of the mouth, and ready to invade the lungs when the entrance-door is no longer barred to them.

There is, however, another form of catarrhal pneumonia which is peculiar to grip, and resembles more the hypostatic and congestive form which we see in other fevers, although it has features of its own which distinguish it even from the latter. Bacteriological research has shown that in this form it is not so much Fraenkel's diplococcus as the streptococcus pyogenes and the staphylococcus aureus which infest the sputum. The patient seems often in a fair way of recovery when this insidious form of broncho-pneumonia begins, sometimes with a

fresh rise in the temperature. It often occurs after undue exposure to cold, or when the patient has prematurely resumed his ordinary occupation. The patient has no rigor, but feels chilly, and perspires unduly. The temperature may be normal in the morning, but rises in the afternoon, and may be 104° in the evening. The breathing may at first be easy, without cough or expectoration; but auscultation shows in a small place, perhaps not larger than a crown-piece, some crepitant râles, which sometimes change their place from day to day, there being less actual inflammation and hepatisation than congestion and catarrh. The breathing is therefore not so tubular as in ordinary pneumonia; there is no marked dulness, and what there is may vary from day to day. The sputum is not that of ordinary pneumonia, but more serous and sanguinolent. Eventually there is complete loss of appetite, distension of the abdomen, and foetid diarrhoea. The heart's action is interfered with, the pulse getting unduly quick, irregular, and intermittent. There is much quiet delirium, and the condition resembles typhoid. The affection usually lasts from two to six weeks, and death is either preceded by coma and Cheyne-Stokes's respiration, or is more sudden, from loss of cardiac power and syncope. Where the

patient recovers, convalescence is generally extremely tedious, and often incomplete. I have known patients to look twenty years older after such an attack, and to have permanently lost all the energy and freshness which formerly distinguished them.

The differences which I have just pointed out as existing between the symptoms of ordinary catarrh and pneumonia on the one hand, and the corresponding processes as part and parcel of influenza on the other hand, are so striking that we are driven to look for the latter to a different etiological factor; and I contend that congestion or inflammation of the nerves supplying the respiratory mucous membranes and lung-tissue by the action of the grippo-toxine is the only cause which will satisfactorily account for the phenomena which we observe.

The nutrition and secretion of the upper portion of the air-passages, including the membranes of the eyes, are under the influence of the fifth pair of cranial nerves; which derives its trophic and secretory elements from its numerous anastomoses with the cervical sympathetic nerve. Experimental division of the fifth nerve is known to cause, in the first instance, circumscribed necrosis of the cornea, with detachment of epithelium and corneal

corpuscles, whereby an opacity is produced. This necrotic patch then acts as an irritant, and leads to inflammation of the cornea, conjunctiva, and the other structures of the eye. Ulceration of the mouth, lips, tongue, and hard palate, is another consequence of section of the fifth. On the other hand, *irritation* of the fifth nerve, through neuritis or pressure of a tumour, gives rise to a great many other symptoms. I have described these fully in a paper read before the Royal Medical and Chirurgical Society in 1868, and published in its Transactions for 1869, and which was based on a case of bilateral neuritis of the fifth nerve, which had then been under my care. Amongst the symptoms present in that case, only those apply to our present purpose which show the condition of the mucous membranes supplied by that nerve. There was hypersecretion of conjunctival mucus, the cornea being covered with streaks and shreds of mucus, which gave a peculiar death-like appearance to the eyes. In the mucous membrane of the nose there was likewise hypersecretion, which had led to thick scabs filling up the nostrils, the mucus being so acrid that on running down to the lips it had made the skin of the sulcus naso-labialis and part of the lip beyond this sulcus quite sore, and had caused the moustache

to fall out there. There had also been great tendency to nasal hæmorrhage. In the mouth the hypersecretion of mucus was so excessive as to oblige the patient to have a pocket-handkerchief constantly applied to it, in order to prevent the liquid from running down the chin ; and the lips appeared covered with froth, such as we see in a patient who is in an epileptic fit. There was also ulceration of the tongue and mouth, and tendency to hæmorrhage from the gums.

Irritation of the fifth nerve is therefore seen to give rise to catarrh of all the mucous membranes supplied by it ; and I consider that the catarrh of the upper portion of the air-passages, which we see in the so-called catarrhal form of grip, is owing to irritation of that nerve by the grippo-toxine. The loss of smell and taste, which is so frequently noticed in these cases, is due to the same cause, as the altered secretion in the nasal fossæ does not allow the fibres of the olfactory nerve to be duly impressed by odoriferous substances. The glossitis, which is sometimes seen in grip, has also a nervous origin ; for glossitis has been seen in severe cases of neuralgia of the fifth, where the congestion of the tongue is sometimes so severe that the organ is constantly kept protruded from the mouth. Eruptions of herpes zoster and sub-acute

inflammation of the periosteum, parotitis, and other inflammatory affections have likewise been observed, together with falling out of the teeth, glaucoma, and certain acute inflammations of the eye, of which I should like to speak more fully did space permit, as they beautifully illustrate the neurotic theory of grip. I cannot, however, now dwell on this subject, and will, therefore, only say that the observations of Galezowski and others on the keratitis of grip, show most plainly the neurotic origin of that inflammation, as the symptoms differ considerably from other forms of keratitis, and are almost identical with those described by Senftleben many years ago as occurring after section of the fifth nerve. The keratitis of grip, being thus shown to be of a peculiar character, has also been found to require an entirely different treatment from that adopted in other forms of keratitis.

In the same way as the nutrition and secretion of the upper portion of the air-passages are under the influence of the fifth nerve, the nutrition and secretion of the lower portion of the tract, from the pharynx down to the lungs, are under the control of the vago-accessory nerve, which like the fifth, has numerous anastomoses with the sympathetic throughout its course. The peculiar hacking cough to which I have drawn attention, I would ascribe

more especially to congestion or inflammation of the cough-centre in the bulb, which is connected with the larynx by the superior laryngeal nerve.

There are few points in experimental physiology which have been so carefully studied ever since the times of Valsalva and Morgagni down to the present day, as the lung affection which follows section of both vago-accessory nerves. Suffice it to say that the consequence of this proceeding in all animals, birds alone excepted, is broncho-pneumonia, as shown by hyperæmia of the mucous membranes, reddening of the lung-tissue, extensive serous effusion, turbidity and swelling of the epithelial cells, collapse of individual parts, more especially in the upper lobes, precipitates of crowds of white blood-corpuscles which have emigrated, and vesicular and vicariating emphysema. Paralysis of the vago-accessory nerves renders the glottis unable to close completely, and thus to separate the digestive from the respiratory tract, so that not only particles of food, but what is even more dangerous, the fluids of the mouth which always contain bacteria, enter the larynx and the lungs, and there act as excitors of inflammation. Death in three or four days is the inevitable result of division of these nerves in most animals, but the cause of death is as yet somewhat

doubtful. It cannot well be the broncho-pneumonia which kills, for birds die after the operation, although no lung-affection occurs in them; and it seems most probable that death is owing to a variety of troubles caused by the removal of so important and complex a nervous mechanism. Thus the complete cessation of the glycogenic function of the liver, which results from this operation, may contribute to the fatal result; and another cause is no doubt the gradual exhaustion of the respiratory centre in the bulb. The centripetal fibres of the vago-accessory nerves have a regulating influence on the respiratory centre; and this influence is suddenly removed by vagotomy. The consequence is that breathing becomes very much slower, the inspiration is rendered tetanic and the expiration active, thus entailing great muscular efforts. There is, therefore, a total change in the normal type of respiration, which leads in its turn to considerable alterations in the circulation of the blood. The work that has to be done by the bulb is rendered so much more laborious that we should naturally expect exhaustion to set in sooner or later; and this is what actually occurs in the later stages of the broncho-pneumonia of grip when the patient is unable to rally. Birds die after vagotomy in eight or ten days with

the symptoms of inanition, and the heart, liver, stomach, and muscles are then found to have undergone fatty degeneration, showing plainly the influence of the pneumogastric nerve on the nutrition of those parts.

Let us now consider at what part of the course of the fifth and the pneumogastric nerves the irritant lesion produced in them by the grippo-toxine is situated. It seems to me evident that this lesion, whether congestive or inflammatory, must be very high up, as the symptoms generally implicate the whole extent of the area which is under the influence of these nerves. Moreover their simultaneous affection, which occurs in the catarrhal form of grip, would lead us to assume a locality where they are lying close together. The two pairs of nerves are in closest contact however in the uppermost portion of the spinal cord and bulb, where they originate with two nuclei, a smaller motor, and a larger sensitive one. The motor nuclei consist of small grey masses lying on the top of the anterior grey cornua of the cord, beneath the intermediary tract of the bulb, and in the middle stratum of the pons; while the sensitive nuclei are situated on the prolongation of the posterior grey cornua of the cord and the tubercle of Rolando, at the sides of the floor of the fourth ventricle. Irritation of this

portion of the bulb is therefore shown to account for the symptoms, observed in the catarrhal form of grip, just as irritation of the vasomotor and other centres in the bulb will account for the symptoms of the nervous variety of grip.

I have mentioned that in my case of bilateral neuritis of the fifth nerve, there was great tendency to hæmorrhage from the mucous membranes affected, particularly the nose and gums; and this observation leads me to consider another set of symptoms which is apt to occur in grip, and of which I have not yet spoken, viz., the *hæmorrhages* which may occur in various parts.

Wherever there is a high degree of congestion, this is apt to be followed by hæmorrhage, through bursting of the over-distended blood vessels; and seeing the all but universal prevalence of congestion in grip, it cannot be a matter of surprise that hæmorrhage in almost all organs of the body should have been frequently noticed during the attack of influenza. The observation to which I have just referred, however, shows the direct dependence of a hæmorrhagic tendency upon nerve-irritation, and will thus aid us materially in understanding its occurrence in the cases under consideration.

The most frequent form of hæmorrhage in grip is

undoubtedly epistaxis, which has by some observers been seen in 30 to 35 per cent. of their cases, and has sometimes been so profuse that it placed the patient's life in jeopardy. Bleeding has also occurred from the gums, the external and middle ear, the bronchial tubes and lungs, the stomach and bowel, the womb and the kidneys. Purpura hæmorrhagica has been seen by several observers, and Pick has described a case of hæmorrhagic diathesis, which occurred in a youth, aged 19, who had been in perfect health before he was seized by grip. The symptoms were profuse epistaxis, hæmorrhage from the gums, hæmatemesis and bleeding from the bowel, hæmorrhage in the subcutaneous cellular tissue of the body and limbs, severe headache, coma, and paresis of the left side. The patient died, and the autopsy showed several small clots in the membranes of the brain, while the lateral ventricles, the Sylvian aqueduct, and the fourth ventricle, were distended with blood. In the right occipital lobe there was a cavity of the size of an orange, filled with blood and *débris* of tissue. Hæmorrhage was also found to have occurred into the pericardium, the cellular tissue of the pharynx, and the stomach. It is clear that such a widely-spread hæmorrhagic tendency must have a central cause, which

I contend to be the specific irritation of the vaso-constrictor centre in the bulb.

3. *Gastric Form of Influenza.*

In a large number of cases of grip, the digestive organs appear to escape the morbid influence. While the patient is extremely ill, restless, and in pain, the tongue may be clean, the appetite good, and the bowels regular. He readily takes his beef-tea, milk, and refreshing drinks, and as soon as the fever has subsided, develops the heartiest appetite. In other instances, however, we find the symptoms of gastric catarrh; the tongue is dirty and slimy, and denuded of its epithelium, or red and dry. There is loss of appetite, thirst, nausea, tenderness in the epigastrium, and either constipation or diarrhœa. But it is not such comparatively mild cases which are considered to belong to the gastro-intestinal form of grip; indeed, the symptoms of this latter are far more severe. There are not only fever and headache, as in the other forms of the disease, but true gastric crises, such as we see them in locomotor ataxy. There is at first nausea and retching, and then violent and incessant vomiting of food, mucus, serum, bile, and blood. The quantity of vomit is much greater than can be accounted for by what the patient may have been

eating or drinking. There is also gastric uneasiness, cramp, and intense pain in the epigastrium and all over the abdomen. The vomiting is sometimes incessant, and everything that is taken is at once brought up again. During such a crisis the pulse is often slow, falling sometimes to thirty beats, or even less, in the minute.

In other cases the bowel may suffer severely, there being the symptoms of dysentery, or cholera. The patient is seized with violent colicky abdominal pain, and severe diarrhoea, with or without vomiting. He may have twenty or thirty motions during the day, the discharge being at first foetid and bilious, while after a time nothing but mucus and blood are passed; or there may be the rice-water evacuations of cholera. The patient is voiceless and prostrate, has a choleraic aspect, and cramps in the legs. Sometimes there is complete paraplegia, and coma may be an early symptom. When the patient survives the attack, convalescence is exceedingly slow; there is extreme debility and emaciation; and digestion often remains impaired to such an extent that the least error in diet leads, weeks or months afterwards, to a return of gastric or intestinal disturbance.

The gastric crises which I have just described, coming on as they do without any other cause except the invasion of the system by the grippo-toxine, point most unmistakably to severe congestion of the vomiting centre in the bulb, which may be affected not only by stimulation of the central end of the vagus, but also by that of many afferent fibres in the same nerve. Faradisation of the central end of the vagus causes vomiting, and arrests urinary secretion. Indeed, the pneumogastric regulates not only the secretion of the gastric juice, but also the motility of the stomach, giving fibres to the mucous membrane as well as to the muscular coat of the viscus, besides which it presides over the glycogenic function of the liver, the action of the pancreas, and even that of the intestines. On the other hand, the whole vascular area of the abdominal cavity is likewise under the influence of the splanchnic nerves, which unite with the phrenic and right vago-accessory nerve to form the coeliac plexus, from which spring the phrenic, hepatic, splenic, mesenteric, renal, and other plexuses. It may thus be readily understood that a shock given to the nucleus of the vago-accessory nerve in the bulb, may be transmitted to any one of the abdominal organs by the nervous path just indicated, and that it may cause more

especially the intestinal crises of which I have just spoken.

Having thus traced the immense variety of symptoms occurring in the different forms of influenza to irritant poisoning of the bulb and the nerve nuclei contained in it, one other question only remains for me to answer, viz. :—Why should the grippo-toxine tend to attack with preference the parts I have mentioned? To that question I can only reply by pointing to analogous facts which have long been known, showing the existence of elective affinities of other poisons to other portions of the nervous system. Let me remind you that ergot of rye attacks with preference the posterior columns of the spinal cord, while lathyrus cicera lays hold in a similar manner of the lateral columns, and lead seeks out the anterior grey cornua of the same organ. With such striking instances before us, it may appear less surprising that the grippo-toxine should select for its point of attack another strictly circumscribed portion of the nervous system, the integrity of which we know to be of the first importance for the various phenomena of life.

In conclusion, I trust that the views of the pathology of grip, which I have laid before you, may lead to a

better comprehension and appreciation of the, at first sight, apparently incongruous phenomena which have been observed in the course of such epidemics as we have recently passed through. Let me at the same time express the hope that before long some junior Fellow of this Society, well versed in the methods of bacteriological research, may succeed in discovering the true micro-organism of grip, in isolating the toxine secreted by it, and in finding the anti-toxine capable of neutralising the poison of grip, and thus securing immunity against the latter. Until this has been attained, I would recommend, in case another epidemic should be at our doors, *wholesale protective re-vaccination of the population* with animal lymph, which seems, according to data furnished by Goldschmidt, to have been the efficient agent in lessening the occurrence and fatality of influenza in the German Army, where re-vaccination is systematically enforced, when compared with the prevalence of the same disease in the civil population.

Now the general conditions of life amongst the troops rather tend to favour than to hinder the spread of such an epidemic amongst them, as they are constantly exposed to the inclemencies of the weather, have to undergo great fatigues, are on the whole badly fed, and

sleep in over-crowded dormitories; yet in spite of all these drawbacks, it was found that while influenza affected 42 per cent. of the civil population of Berlin, and as much as 64 per cent. of that of Paris, its prevalence in the German Army amounted only to 11·1 per cent. A number of garrisons were entirely spared, while the civil population of the towns where they were stationed suffered severely; and no garrison was ever affected where the civil population enjoyed immunity. Apart from this the average duration of the illness was comparatively short in the army, viz., 5·65 days, while unfavourable complications occurred only in 3·1 per cent. of those affected. The death-rate was also smaller, being twelve times less than that of the civil population of Berlin, and twenty-five times less than that of Paris. It was likewise found that amongst the troops those suffered chiefly who had not been recently re-vaccinated.

These observations find a singular corollary in the fact, which has been observed over and over again, that infants and young children are proof against influenza. What else is likely to be the cause of this except that they have acquired immunity by recent vaccination?

For in the morn and liquid dew of youth,
Contagious blastments are most imminent.

On the other hand, we know that the school children who have presumably not been re-vaccinated, and in whom the protective power of early vaccination has been lost, suffer severely from grip. I am also in possession of a number of facts, showing that in the midst of a crowd of grip-stricken people, a small cluster of persons, who had for some particular reason been recently re-vaccinated, remained untouched by the epidemic, although they mingled freely with those affected; while in some establishments every one was struck down except those children and adults who had been re-vaccinated a short time before.

The facts and references which I have placed before you appear to be of far-reaching importance; and although it still remains to be proved that we are able to stamp out influenza by resorting to re-vaccination, there seems good reason for asking you to proceed to this task, with the view of obtaining a further advance towards that great ultimate end of all our labours—the prevention of disease.

If you consider the immense amount of individual suffering entailed by the attack of influenza, the lives lost,

the health and working powers of thousands of persons destroyed for all time, as well as the distress caused to whole families by the sudden loss of the bread-winner through this scourge, you will no doubt agree with me in thinking that the slight inconvenience caused by re-vaccination will appear like a feather in the scale when weighed against the evils of influenza, which it is our duty to prevent from occurring in the community.

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